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Award Number: W81XWH-04-1-0195

TITLE: Endogenous 6-Hydroxymelatonin Excretion and Subsequent Risk of Breast Cancer: A Prospective Study

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REPORT DATE: March 2007

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
01-03-2007	Annual	1 Mar 2006 – 28 Feb 2007

4. TITLE AND SUBTITLE

Endogenous 6-Hydroxymelatonin Excretion and Subsequent Risk of Breast Cancer: A Prospective Study

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-04-1-0195

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Italian National Cancer Institute
00144 Rome, Italy

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The prevalence of breast cancer is greatest in industrialized regions and exposure to light at night has been proposed as a potential risk factor. Modulation of melatonin secretion by light has been implicated in the causal pathway linking exposure to light and breast cancer risk. Recent evidence indicates that melatonin is a natural oncostatic agent capable of functioning through a variety of anti-proliferative, anti-oxidative, and immunostimulatory mechanisms. We conduct a study to investigate the association of prediagnostic melatonin production and subsequent breast cancer risk in a prospective cohort study, the Italian ORDET study. Thus, prediagnostic melatonin production will be measured as urine levels of the 6-hydroxymelatonin sulphate (6-OHMS), its primary enzymatic metabolite, in 12-hour urine (overnight) collection. The study will be conducted as a nested case-control study. We expect 533 breast cancer cases among cohort members during the 17 year-follow-up period. Four controls will be matched to each case on age, menopausal status, recruitment center and time of recruitment for a total number of 2,132 control subjects. This study would be the first one analyzing the potential effect of melatonin on breast cancer risk. It will provide important data on risk factors that are likely key to the development of this disease at great public health impact.

15. SUBJECT TERMS
Breast cancer, Melatonin, Epidemiological Study

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
U	U	U	UU	20	**19b. TELEPHONE NUMBER** *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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INTRODUCTION

Melatonin (N-acetyl-5methoxtryptamine) is synthesized and released by the pineal gland in response to darkness. Thus, melatonin displays a strong variation during a 24-hour period: its serum levels are low during daylight hours and high at night. The health effect of chronic alteration of this circadian rhythm in humans has received relatively little attention. There is strong evidence to indicate that melatonin acts as a natural oncostatic substance (Blansk, 1993). Consistent experimental evidence, from both *in vitro* and *in vivo* studies, identified specific anti-carcinogenic functions of melatonin such as anti-proliferation, anti-oxidation, and immunostimulation functions (Brzezinski, 1997; Panzer and Viljoen, 1997; Reiter et al, 1997).

Environmental factors that reduce nocturnal exposure to melatonin may increase breast cancer risk by increasing levels of estrogens, by increasing exposure to oxidative stress and by reducing immune function (Cohen et al, 1978; Stevens, 1987). Nighttime plasma melatonin is reported to be lower in women affected with estrogen-receptor-positive breast cancer in comparison with women affected by other pathologies (Tamarkin et al, 1989). Melatonin was also lower in breast cancer cases than in women with benign breast disease (Bartsh et al, 1989). We are conducting a study to evaluate the relationship between melatonin and breast cancer using data from a prospective cohort study in which several sources of possible biomarker variability have been controlled by study design. We measure pre-diagnostic urine levels of the main melatonin metabolite, **6-OHMS**, in urine stored at –80º C during the 17 year follow-up period. At its completion, the study will allow us to investigate the role of prediagnostic melatonin as a potentially important factor underlying the association between environmental and life-style factors with breast cancer.

BODY OF REPORT

In accordance with the Statement of Work we completed determinations for the samples from post-menopausal women and are now determining samples from pre-menopausal women.

Background

The Lombardy Cancer Registry (LCR) conducts the follow-up of the ORDET cohort. LCR, established by the Regional County Council for Health and supervised by the Epidemiology Unit at the National Cancer Institute in Milan, has been operating since January 1, 1976. LCR registers and includes in the incidence figures all malignant tumors, according to the categories 140-208, chapter two of the International Classification of diseases, ninth revision (ICD-9). The ORDET study and LCR reside in the same institution at the Italian NCI in Milan (Instituto Nazionale per lo Studio e la Cura dei Tumori). The LCR searches for cases actively, using various information sources, primarily hospital clinical records and pathology department records. The Italian National Health Service (NHS) provides health assistance for all citizens. Most health care services are public. Private facilities are also partially supported by NHS. Among all breast cancer cases arisen among residents of Varese Province, only 1.3% is known to the registry on the basis of death certificates only, and 99% of breast cancer cases are microscopically verified. LCR incidence data are regularly published in the “Cancer Incidence in Five Continents” (International Agency for Cancer Research-World Health Organization, 1982-1997; 1998-2002) and in several international publications on population-based cancer survivals (Eurocare Study I, 1995; Eurocare Study II, 1999). In the context of these studies on cancer survival, the LCR collects clinical information of cancer cases. Among this information, LCR collects the receptor status of the breast cancers identified in the population. This variable is included in the data analysis of the present study.

The end of follow-up is determined by death, immigration outside Italy or last day of the follow-up: in the case of the present application the last day of the follow-up was June 30, 2006. The latency period between cancer diagnosis and detection by the LCR is 6 months.

The present study was based on the projected incidence of cancer in the cohort by June 30th, 2006, with 533 expected breast cancer cases.

At present we are conducting the melatonin determinations for each identified case and the four related controls. Study protocols have been developed and discussed. Determinations have been completed for samples from post-menopausal women and we are now determining samples fom pre-menopausal women.

Methods

Breast Cancer Cases: Breast cancer cases are women with histologically confirmed invasive breast cancer diagnosed after their recruitment (date at interview) to the ORDET cohort and before the end of the last follow-up period.

Control Subjects: Eligible controls are all be women free of cancer at the time of the diagnosis of the case. For each breast cancer case, four controls are randomly chosen after matching for sources of hormone variability: a) age; b) same recruitment center to exclude differences due to transportation of samples to laboratory; c) recruitment date to control for the effect of long-term preservation of sera; d) daylight saving period to allow for possible changes in circadian rhythm.

12 Hour Urine Collection: For urine collection at baseline, each participant was asked to empty her bladder before retiring at 7:00 PM, and to collect any urine voided during the night, as well as the first morning void at 7:00 AM. Participants then delivered urine between 7:30 and 9:30 AM to the ORDET recruitment center, where it was filtered and stored at –80°C. Urine samples have not been thawed up to now. Therefore, there will be no effects of freezing-thawing cycles and we will thaw urine for this study at the time of the proposed 6-OHMS determinations.

Analytical Methods: Melatonin production at baseline is evaluated through the urine excretion of 6-OHMS, its primary enzymatic metabolite using radioimmunoassay method (Bühlmann Laboratories AG, Switzerland). We correct concentration levels of 6-OHMS for creatinine excretion. There is evidence that total nocturnal production of melatonin is well correlated with levels of 6-OHMS in 24 hour urine samples and with morning urine samples (Markey et al, 1985 and Bojkowski et al., 1987; Cook et al., 2000). 6-OHMS shows good reliability and low intra-individual variability, at least over a short time period (Bojkowski et al., 1987), reflecting a stable rate of melatonin production in the same individual (Bojkowski et al., 1987; Arendt J, 1978). Finally, 6-OHMS is extremely stable in urine stored at -20˚C and at -12˚C for at least two years of cryopreservation (Bojkowski et al., 1987).

Biological specimens of all cases and matched controls are retrieved from the ORDET biological specimen bank and sent, on dry ice, to the Hormone Research Laboratory, at the Department of Preventive and Predictive Medicine of the Istituto Nazionale Tumori under the direction of Dr. Giorgio Secreto. The Laboratory is located in the same building as the ORDET specimen bank. Stored samples from cases and controls are handled identically and assayed together in the same batch. Each batch includes cases and their matched controls. Laboratory personnel are blinded to case control status of samples. In addition,

we include blind control duplicates for 5% of the samples in each batch. All samples are assayed in duplicate.

The analytical determinations for all the biomarkers will be completed in the next year.

KEY RESEARCH ACCOMPLISHMENTS

- Completed the follow-up of the prospective cohort study
- Set up the nested case-control study
- Study protocols developed
- Melatonin determinations for cases and controls have begun and will be completed in the next year.

REPORTABLE OUTCOMES

Publications and Presentations

We have published a paper based on the research developed during the evaluation of the bioassay method reliability:

Barba M, Cavalleri A, Schünemann HJ, Krogh V, Evangelista A, Secreto G, Micheli A, Zhou Q, Fuhrman B, Teter B, Berrno F, *Muti P.* **Reliability of urinary 6-sulfatoxymelatonin as a biomarker in breast cancer.** ***The International Journal of Biological Markers*****.** ***21(4):242-5, 2006***

In 2006-2007, Dr. Muti has published other papers on hormones and cancer, as listed below:

1. *Barba M, McCann S, Nie J, Vito D, Stranges S, Fuhrmann B, Trevisan M, Muti P, Freudenheim JL. *Perinatal Exposures and Breast Cancer Risk in the Western New York Exposures and Breast cancer (WEB) Study.* Cancer Causes Control 17(4): 395-401, 2006

2. McCann SE, Kulkarni S, Trevisan M, Vito D, Nie J, Edge S, Muti P, Freudenheim JL. *Dietary lignan intakes and risk of breast cancer by tumour estrogen receptor status.* Breast Cancer Research and Treatment 99(3):309-11, 2006

3. Cavalieri E, Chakravarti D, Guttenplan J, Hart E, Ingle J, Jankowiak R, Muti P, Rogan E, Russo J, Santen R, Sutter T. *Catechol Estrogen Quinones as Initiators of Breast and Other Human Cancers: Implications for Biomarkers of Susceptibility and Cancer Prevention.* BBA-Reviews 2006 1766(1): 63-78, 2006

4. Zeleniuch-Jacquotte A, Ludin E, Micheli A, Koenig KL, Lenner P, Muti P, Shore RE, Johasson I, Krogh V, Lukanova AK, Stattin P, Afanasyeva Y, Rinaldi S, Arslan A, Kaaks R, Berrino F, Hallmans G, Toniolo P, Adlercreutz H. *Circulating Enterolactone and risk of endometrial cancer.* The International Journal of Cancer 119(10):2376-81, 2006

5. Han D, Nie J, Bonner MR, McCann S, Muti P, Trevisan M, Ramirez F, Vito D, Freudenheim JL. *Lifetime adult weight gain, central adiposity and the risk of pre- and postmenopausal breast cancer in the Western New York Exposures*

and Breast Cancer Study. The International Journal of Cancer 119(12):2931-7, 2006

6. Barba M, Cavalleri A, Schünemann HJ, Krogh V, Evangelista A, Secreto G, Micheli A, Zhou Q, Fuhrman B, Teter B, Berrno F, Muti P. *Reliability of urinary 6-sulfatoxymelatonin as a biomarker in breast cancer.* The International Journal of Biological Markers. 21(4):242-5, 2006

7. Muti P, Rogan E, Cavalieri E. *Androgens and Estrogens in the Etiology and Prevention of Breast Cancer .* Nutrition and Cancer 56(2):247-52, 2006

8. Browne R, Koury S, Marion S, Wilding G, Muti P, Trevisan M. *Accuracy and biological variation of human serum paraoxonase 1 activity and polymorphism (Q192R) by kinetic enzyme assay.* Clin. Chem. Feb;53(2):310-7, 2007.

9. McCann SE, Wactawski-Wende J, Olson J, Ovando B, Nowell S, Davis W, Carter L, Muti P, Shields PG, Freudenheim JL.. *Changes in 2-hydroxyestrone and 16alpha-hydroxyestrone metabolism with flaxseed consumption: modification by COMT and CYP1B1 genotype.* Cancer Epidemiology Biomarkers and Prevention 16(2):256-62, 2007

10. McCann SE, McCann WE, Hong C, Marshall JR, Edge S, Trevisan M, Muti P, Freudenheim JL. *Dietary patterns related to glycemic index and load and risk of pre- and postmenopausal breast cancer in the Western New York Exposures and Breast Cancer (WEB) Study.* (accepted for publication in The American Journal of Clinical Nutrition)

11. Sant M, Allemani C, Sieri S, Krogh V, Menard S, Tagliabue E, Nardini E, Micheli A, Crosignani P, Muti P, Berrino F. *Salad vegetables dietary pattern protects against HER-2-positive breast cancer: A prospective Italian study.* Int J Cancer. (Epub ahead of print)

Dr Muti has also presented new results from other studies at the Annual Meeting of the American Association for Cancer Research as well as other conferences:

1. Barba M, Terrenato I, Fuhrman B, Teter B, Schunemann H, **Muti P.** *Secondary sexual characteristics and body size at different ages in relation to risk of prostate cancer: results from a case-control study* Annual Meeting American Association for Cancer Research,Washington, April 2006

2. McCann SE, **Muti P**, Vito D, Edge SB, Trevisan M, Freudenheim JL. *Dietary lignan intakes and risk of breast cancer by tumor estrogen receptor status.* Annual Meeting American Association for Cancer Research, Washington, April 2006

3. Fuhrman BJ, Teter BE, Barba M, Byrne C, Cavalleri A, Grant BJ, Horvath P, **Muti P**. *Soy intake and mammographic density in postmenopausal women: Modification by equol status.* 5th Annual Meeting American Association for Cancer Research, Boston, November, 2006

4. Teter BE, Fuhrman BJ, Barba M, **Muti P**. *Aspirin Use and Mammographic Breast Density as a Marker of Breast Cancer Risk in Postmenopausal Women*. 5th Annual Meeting American Association for Cancer Research , Boston, November, 2006

5. Teter BE, Fuhrman BJ, Barba M, **Muti P**. *Nocturnal 6-Sulfatoxymelatonin and Mammographic Breast Density as a Marker of Breast Cancer Risk in Postmenopausal Women.* 5th Annual Meeting American Association for Cancer Research, Boston, November 15, 2006

6. Meneghini E, Secreto G, Krogh V, Crosignani, **Muti P**, Berrino F, Micheli A. *Biological adjustment approach in synchronizing blood sampling over menstrual cycle. The experience with progesterone and breast cancer risk in pre-menopausal ORDET women.* Annual Meeting of the Cancer Registries of Latin Language (GRELL), Montreal, May 2007 (abstract has been accepted)

7. Akl E, Cook D, **Muti P**, Puhan M, Montori V, Guyatt G, Schünemann H. *Systematic evaluation of the methodology of randomized controlled trials of anticoagulation in patients with cancer.* 15th Cochrane Colloquium, São Paulo, 23-27 October, 2007 (abstract has been accepted)

In addition, Dr. Muti has several other manuscripts submitted for publication on hormone and related factors and cancer.

CONCLUSIONS

We are continuing the hormone determinations phase for this grant. Therefore, there are no conclusions to report at this time.

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